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(71) Applicants *(for all designated States except US)*: **SHAYEN MEDICAL LTD.** [IL/IL]; 9 Hakotzer Street, 47411 Ramat Hasharon (IL). **KEREN, Gad** [IL/IL]; 11 Simcha Holzberg Street, Kiryat Ono 55022 (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARUCH, David** [IL/IL]; 9 Hakotzer Street, 47411 Ramat Hasharon (IL). **ROTMAN, Avner** [IL/IL]; 21 Eisenberg Street, 76289 Rehovot (IL).

(74) Agents: **SANFORD T. COLB & CO.** et al.; P.O. Box 2273, 76122 Rehovot (IL).

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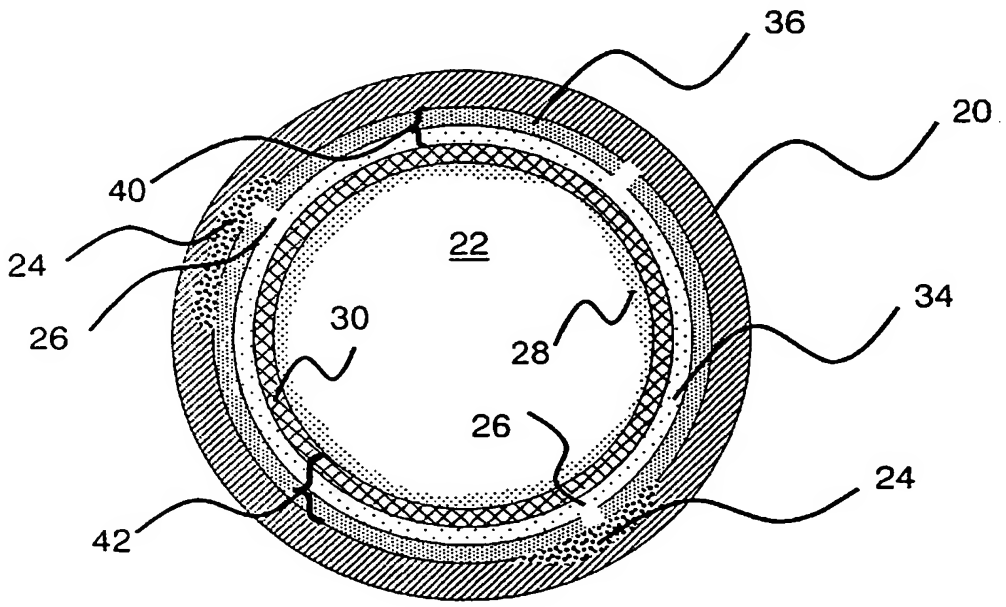
(54) Title: DRUG-ELUTING MEMBRANE FOR CORONARY ARTERY STENT



(57) Abstract: A membrane (40) is provided for implantation in a coronary artery (20) of a patient. The membrane preferably includes a substantially-cylindrical elastometric polyurethane body, adapted for subsequent application to a coronary artery stent (30). The body of the membrane typically includes one or more pharmaceutical products, e.g., an anti-inflammatory agent and an anti-proliferative agent, optionally disposed on different respective layers (34, 36) of the membrane.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DRUG-ELUTING MEMBRANE FOR CORONARY ARTERY STENT

FIELD OF THE INVENTION

The present invention relates generally to treatments for cardiovascular pathologies, and specifically to implantable apparatus for treating cardiovascular pathologies.

BACKGROUND OF THE INVENTION

The clinically-significant rate of recurrence of stenosis of a coronary artery following corrective surgery is as high as 40% within one year following the performance of any of a range of commonly-practiced angioplasty techniques, such as balloon angioplasty, atherectomy catheterization, laser angioplasty and stent implantation. Attempts have been made to minimize the restenosis rate using medications, coatings applied to implantable stents, and other special local treatments, but these have had only limited success.

Approximately 100,000 patients worldwide undergo repeat treatments every year because of restenosis following the implantation of a stent. Neointimal hyperplasia (i.e., the growth of the arterial layer of smooth muscle cells around the ends of an implanted stent or through the metal mesh and into the lumen of the stent) is the main cause of restenosis of a stented blood vessel. Stents effectively eliminate the closure of a blood vessel following an angioplasty procedure, but tend to encourage the process of neointimal hyperplasia, and, consequently, restenosis of the vessel. It is hypothesized that the wall injury inherent in any coronary angioplasty leads to the exposure of underlying atheromatous tissue and the elution of macromolecules, among them proinflammatory mediators.

These attract macrophages which migrate into the vascular wall to release further cytokines, metalloproteinases and growth factors that play a role in initiating the restenotic process.

An article by Mudra et al., entitled, "Serial follow-up of the optimized ultrasound-guided deployment of Palmaz-Schatz stents: In stent neointimal proliferation without significant reference segment response," *Circulation,* 1997; 95:363-370, which is incorporated herein by reference, reports that the predominant mechanism of in-stent restenosis is neointimal proliferation.

An article by Marin et al., entitled, "Effect of PTFE covering of Palmaz stents in the development of intimal hyperplasis in human iliac arteries," *J. Vasc. Inerv. Radiol.*, 1996; 7:651-656, which is incorporated herein by reference, reports reduced cell proliferation in PTFE (Teflon)-coated stents.

An article by Yuan et al., entitled, "The effect of nonporous PTFE-covered stents on intimal hyperplasia following balloon arterial injury in minipigs," *J Endovasc Surg*, 1998 Nov; 5(4):349-58, which is incorporated herein by reference, reports the results of an experimental study investigating the ability of a nonporous polytetrafluoroethylene (PTFE) covering on a metallic stent to retard the development of neointimal hyperplasia (NIH). PTFE-covered stents were found to retard NIH at 4 weeks, but only at the midportion of the devices; the covering did not prevent neointimal pannus ingrowth at the proximal and distal ends.

An article by Drachman et al., entitled, "Neointimal thickening after stent delivery of paclitaxel: Change in composition and arrest of growth after six months," *J. Am. Coll. Cardiol.*, 2000 December; 36(7):2324-2332, which is

incorporated herein by reference, notes that copolymer coated stents permit sustained paclitaxel delivery in a manner that reduces neointimal hyperplasia for months after stent implantation.

The following patents, which are incorporated herein by reference, describe apparatus and methods for treating cardiovascular disorders: US 5,916,264 to Van Oepen, US 5,951,586 to Berg, US 6,030,413 to Lazarus, US 6,066,169 to McGuiness, US 6,071,305 to Brown, US 6,080,190 to Schwartz, US 5,985,307 to Hanson, US 6,168,619 to Dinh, US 6,171,609 to Kunz, US 6,197,789 to Grainger, US 6,096,070 to Ragheb, US 6,159,488 to Nagler, and US 6,099,559 to Nolting.

The above-cited US 5,916,264 describes a stent graft with two coaxially-arranged radially-expandable stents, and a flexible, stretchable material layer between the stents. The material layer is formed as a fabric band wound around the inner stent.

The following articles, which are incorporated herein by reference, describe further apparatus and methods for treating cardiovascular disorders:

- "The Jomed covered stent graft for coronary artery aneurysms and acute perforation: A successful device which needs careful deployment and may not reduce restenosis," Campbell et al., *J Invas Cardiol*, 12(5):272-276, 2000
- "Coronary stent grafts covered by a polytetrafluoroethylene membrane," by Elsner et al., *American Journal of Cardiology*, vol. 84, August 1, 1999
- "Membrane-covered stents for the treatment of aortocoronary vein graft disease," Baldus et al., *Catheterization and Cardiovascular Interventions*, 50:83-88 (2000)

- "Self-expandable vascular stent covered with a polyurethane membrane, placed in a thoracic descending aorta of a rabbit," Uematsu et al., *Ann Thorc Cardiovasc Surg*, Vol. 6, No. 2 (2000)
- "Implantation of stents covered by autologous arterial grafts in human coronary arteries: A new technique," Stefanadis et al., *J Invas Cardiol*, 2000: 12:7-12

The above-cited Elsner article notes that the "Jostent" clinical trial results support the use of the Jostent for acute coronary rupture, but that treatment of conventional in-stent restenosis was not associated with a favorable outcome. The above-cited Campbell article also finds that the Jostent may not reduce restenosis. Similarly, the above-cited Baldus article examines the drawbacks of the Jostent, noting that since the stent is made out of two layers of struts, its flexibility is reduced. A particular potential drawback of this device might be delayed endothelialization, as previously described in experimental studies. Such a delay may, in turn, cause thrombotic in-stent vessel occlusions.

Stent grafts are typically used to treat aneurysms and to reconstruct blood vessels. These stent grafts include:

- The Medtronic, Inc., AneuRx stent graft system for the treatment of abdominal aortic aneurysms (AAA's). The AneuRx system uses self-expanding diamond shaped rings to create a friction fit.
- The above-cited US 5,951,586 to Berg describes an intraluminal stent, which has a plurality of recesses. Preferred stents are constructed of films on support structures.
- The above-cited US 6,030,413 to Lazarus describes an intraluminal grafting system which includes a hollow

graft and a distal staple adapted proximate its distal end.

- The above-cited US 6,066,169 to McGuiness describes stents having expandable cylindrical elements and some other modifications, like stent graft devices, wherein a graft is disposed around the periphery of the stent.
- The above-cited US 6,071,305 to Brown describes a directional drug delivery stent, which includes an elongated tubular member having a cavity containing a biologically active agent.
- The above-cited US 6,080,190 to Schwartz describes an intraluminal stent comprising fibrin, which is intended to reduce the incidence of restenosis at the site of vascular injury, such as that secondary to an angioplasty procedure.
- The above-cited US 5,985,307 to Hanson describes a device for the local delivery of a substance into a natural tissue conduit in a mammal's body.
- The above-cited Uematsu article describes a self-expandable vascular stent, covered with a polyurethane membrane, which was placed in a thoracic descending aorta of a rabbit.

In general, current stent grafts are not well-suited for long term implantation in the coronary arteries. The graft material typically causes occlusion-related problems, such as those described hereinabove with reference to the Jostent.

The harvesting, preparation and assembly of human radial arterial grafts for a stent is a very time consuming process. Also, the properties and dimensions of an autologous graft vary, and are not completely controllable.

Boston Scientific Corporation and Cook, Inc. conduct research using paclitaxel-coated coronary stents, which are intended to reduce in-stent restenosis. In the Cook stent, the metal body of the stent is coated with a minute quantity of the drug, which is intended to be gradually released into the cells of the arterial wall, and act to prevent excessive cell regrowth at the site of an angioplasty.

An article entitled, "Performance of a polyurethane vascular prosthesis carrying dipyridamole (Persantin) coating on its luminal surface," by Aldenhoff et al., *J. Biomed. Mater. Res.*, 2001, February; 54(2): pp. 224-233, which is incorporated herein by reference, describes a porous polyurethane vascular prosthesis, which carries a coating of immobilized dipyridamole (Persantin(R)) on the surface of its lumen. Dipyridamole is a potent nontoxic inhibitor of platelet activation/aggregation, and is also a strong inhibitor of vascular smooth muscle cell proliferation. The polyurethane material is also known as Chronoflex(R), and has been used as a vascular access graft.

All of the references cited herein are incorporated by reference.

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide improved methods and apparatus for treating cardiovascular disorders.

It is a further object of some aspects of the present invention to provide improved methods and apparatus for reducing restenosis following surgery.

It is yet a further object of some aspects of the present invention to provide improved methods and apparatus for local delivery of drugs.

It is still a further object of some aspects of the present invention to provide improved methods and apparatus for allowing the selection of one or more drugs for delivery to a cardiac site.

It is an additional object of some aspects of the present invention to provide improved methods and apparatus for allowing the control of a delivery schedule of one or more drugs for delivery to a cardiac site.

It is still an additional object of some aspects of the present invention to provide improved methods and apparatus for increasing the longevity and acceptance of a stent implanted in a coronary artery.

It is yet an additional object of some aspects of the present invention to provide improved methods and apparatus for producing membranes which are compatible with a range of commercially-available stents.

It is also an object of some aspects of the present invention to provide improved methods and apparatus for substantially increasing the quantity of one or more drugs which can be delivered to a site in a coronary artery where a stent is implanted.

It is a further object of some aspects of the present invention to provide improved methods and apparatus for facilitating the growth of endothelial cells so as to line the inner lumen of a stent, while inhibiting neointimal hyperplasia.

It is yet a further object of some aspects of the present invention to provide improved methods and apparatus for creating polyurethane membranes for use with coronary artery stents.

It is still a further object of some aspects of the present invention to provide improved methods and apparatus for perforating a drug-delivery membrane designated for application to a stent.

In preferred embodiments of the present invention, a membrane is produced for subsequent application to a stent. Preferably, the membrane comprises a biocompatible, biostable, highly-elastic polyurethane, and is mixed with one or more drugs, which are, for example, intended to minimize the inflammatory response to implantation of the stent or to prevent restenosis in a coronary artery in which the stent is implanted. Advantageously, use of a polyurethane membrane as provided by these embodiments of the present invention generally facilitates the formation and growth of an endothelial lining on the inner lumen of the membrane and stent. This stands in contrast to some prior art techniques, in which a PTFE membrane is used with a coronary artery stent, because PTFE inhibits the adhesion thereto of endothelial cells.

Notably, and unlike commercially-available stent-based drug-delivery systems for use in a coronary artery, the polyurethane membrane is typically able to deliver a significant quantity of the one or more drugs, e.g., hundreds or several thousands of micrograms of each drug.

By contrast, prior art stents intended for use in a coronary artery typically have a drug applied directly to the stent itself, i.e., as a coating on the metal. The quantity of drug which can be stored in the metal and effectively transferred into the patient is substantially lower than that provided by these embodiments of the present invention, e.g., typically by about one, two, or even three orders of magnitude.

For some applications, the membrane comprises two layers, each including a respective drug or combination of drugs. In a preferred embodiment, the inner layer of the membrane comprises an anti-proliferative drug, intended to reduce neointimal hyperplasia, while the outer layer of the membrane comprises an anti-inflammatory drug, intended to facilitate the healing process of the tissue of the coronary artery following the stent implantation. As appropriate, other drugs, such as steroids, anti-thrombotic drugs, and tissue growth regulating drugs may be integrated into the membrane. It is noted that local application of the one or more drugs minimizes the total dose administered into the patient's body, because substantially all of the drug is administered directly to the lesion, and only small amounts are released systemically. Advantageously, whether one or two layers are used, covering the stent with a membrane typically inhibits that portion of the restenosis which occurs in some prior art coronary artery stents through the struts of these stents.

In both single-layer and multi-layer membranes, the kinetics of the release of the one or more drugs is typically controllable to a significantly greater extent than is possible using coronary artery stents directly coated with a drug. For example, the membrane may be configured such that one of the drugs is released over a

time period spanning less than five hours, while another one of the drugs is released over a period greater than five hours, or even over days, weeks, or months, as appropriate. By contrast, when metal coronary artery stents are directly coated with a drug (a process known in the art), the drug is typically essentially entirely released in a relatively-short time period.

For some applications, the membrane is perforated prior to application to a stent, so as to facilitate the passage of therapeutic materials from the bloodstream to a lesion which may have formed around the stent implantation site. Preferably, the perforation process is additionally configured so as to enhance the growth of the endothelial lining on the inner surface of the stent, e.g., by permitting endothelial cell growth through the pores in the membrane. Further preferably, pharmaceutical products incorporated into the membrane are utilized to inhibit smooth muscle cell proliferation (neointimal hyperplasia) on the inner surface of the stent, which may lead to restenosis and thereby increase the likelihood of a second angioplasty procedure. As appropriate, the membrane perforation may be performed mechanically, chemically, or by laser or other forms of radiation.

Typically, the membrane provided by these embodiments of the present invention is adapted to be applied to any of a range of commercially-available stents, for example, the NIR or NIROYAL stents, manufactured by Medinol, Israel, and distributed by Scimed of Boston Scientific, USA. Because the membrane is typically highly elastic, a single membrane can preferably be fitted even to stents made by different manufacturers which may differ with respect to one or more physical characteristics, such as length, diameter, or expansion ratio (expanded diameter / non-expanded

diameter). The membrane is preferably secured to the stent by a pressure fitting process, although it is to be appreciated that for many applications, other processes may be suitable. Advantageously, pressure fitting a thin membrane to a stent does not produce a bulky or stiff stent, and is generally not associated with tearing of the membrane during expansion of the stent, as may occur using certain prior art techniques in which a membrane is dip-coated directly onto a stent.

In accordance with some preferred embodiments of the present invention, the single-layer or multi-layer membrane is prepared in advance, preferably by a dip-coating process. Subsequently the membrane is removed from the mandrel used for dip-coating and secured to a stent. As appropriate, one or more drugs may be incorporated into the solution(s) in which the mandrel is dipped. By way of illustration and not limitation, for a two-layer membrane, the first solution may comprise an appropriate solvent, polyurethane grains and an anti-proliferative agent, while the second solution may comprise the solvent and polyurethane grains and an anti-inflammatory agent. Alternatively or additionally, one or more pharmaceutical products are applied to either or both surfaces of the membrane subsequent to creation of the membrane.

Advantageously, the dip-coating process produces a membrane without any seams, as are common using some prior art technologies. Moreover, attachment of the preformed cylindrical membrane to the stent is simpler than with prior art rectangular membranes, which are rolled around the stent (i.e., assembled at the time of placement on the stent), in order to form the necessary cylindrical shape.

Preferably, the membrane comprises an elastomer such as Tecoflex 80A (Thermedics, USA), Chronoflex AR

(Cardiotech, USA), or ElastEon 3 (Elastomedic Pty, Australia). These materials, as well as others known in the art, are typically able to stretch more than 500% without suffering structural damage, and are therefore satisfactory for the considerably smaller strains induced during inflation of a stent.

As appropriate, techniques described herein may be substituted by or applied in combination with or separately from techniques described in Israel Patent Application 137,860, entitled, "Coronary membrane covered stent," filed August 15, 2000, which shares common inventorship with the inventorship of the present patent application and is incorporated herein by reference.

There is therefore provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation in a coronary artery of a patient, including a substantially-cylindrical elastomeric polyurethane body adapted for subsequent application to a coronary artery stent.

Preferably, the body includes at least one pharmaceutical product. In a preferred embodiment, the pharmaceutical product includes a pharmaceutical product applied to a surface of the membrane prior to implantation of the membrane in the patient. Alternatively or additionally, the pharmaceutical product includes a pharmaceutical product mixed into the body of the membrane. For some applications, the pharmaceutical product includes an anti-inflammatory agent, an anti-proliferative agent, a steroid, an anti-thrombotic agent, and/or a tissue growth regulating agent.

For some applications, the pharmaceutical product includes at least two distinct pharmaceutical products. In a preferred embodiment, the body includes an inner surface,

adapted to deliver to the patient a first one of the pharmaceutical products, and an outer surface, adapted to deliver to the patient a second one of the pharmaceutical products. For example, the first one of the pharmaceutical products may include an anti-proliferative agent, and the second one of the pharmaceutical products may include an anti-inflammatory agent.

Preferably, the membrane includes at least 100 micrograms of a pharmaceutical product, hardware is capable of passing from the membrane to the patient after implantation of the membrane in the patient. For some applications, at least 500 micrograms of the product, or even greater than 1000 micrograms of the product are included in the membrane.

There is further provided, in accordance with a preferred embodiment of the present invention, a cylindrical membrane for implantation in a patient, including:

an inner layer, including a first pharmaceutical product and adapted for subsequent application to a stent; and

an outer layer, disposed further from an axis of the cylindrical membrane than the inner layer, including a second pharmaceutical product different from the first pharmaceutical product.

There is yet further provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation in a patient, including a cylindrical polyurethane body adapted to be fixed to a coronary artery stent by pressure fitting and to be implanted with the stent in a coronary artery of the patient. Typically, the membrane is adapted for pressure fitting to any one of a

plurality of stents, each having a different respective physical characteristic.

There is still further provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation in a patient, including a cylindrical, substantially-seamless polyurethane body adapted to be fitted to a coronary artery stent and to be implanted with the stent in a coronary artery of the patient.

There is additionally provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation in a patient, including a cylindrical, preformed polyurethane body adapted to be fitted to a coronary artery stent and to be implanted with the stent in a coronary artery of the patient.

There is yet additionally provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation with a stent in a coronary artery of a patient, the membrane including a cylindrical polyurethane body having an inner surface treated so as to facilitate endothelial cell adherence thereto. For example, the body of the membrane may include a pharmaceutical product in a vicinity of the inner surface, which pharmaceutical product is such as to facilitate the adherence. Preferably, the inner surface is also treated so as to inhibit neointimal hyperplasia (NIH). In a preferred embodiment, the body of the membrane includes a NIH-inhibiting pharmaceutical product in a vicinity of the inner surface.

There is still additionally provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation in a coronary artery of a patient, including a cylindrical body which includes a pharmaceutical product and which is adapted for subsequent

application to a stent, the body being adapted to release the pharmaceutical product for at least five hours following implantation of the membrane in the patient. Preferably, the body is adapted to release the pharmaceutical product for at least 24 hours following implantation of the membrane in the patient. Further preferably, the body is adapted to release the pharmaceutical product for at least 72 hours following implantation of the membrane in the patient.

There is also provided, in accordance with a preferred embodiment of the present invention, a membrane for implantation in a coronary artery of a patient, including polyurethane and a biodegradable polymer selected from the list consisting of: polylactic acid, polyglycolic acid, and a copolymer of lactic and glycolic acid, a disposition of the biodegradable polymer in the membrane being such as to: (a) degrade the polymer following implantation of the membrane in the coronary artery, and (b) induce the generation of perforations in the membrane responsive to the degrading.

In a preferred embodiment, prior to implantation, a first portion of the membrane includes a first concentration of the polymer and a second portion of the membrane includes a second concentration of the polymer, different from the first concentration, the first and second concentrations being such as to induce different respective densities of perforations in the first and second portions of the membrane.

The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof, taken together with the drawing, in which:

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a schematic cross-sectional illustration of a membrane applied to a stent and implanted in a coronary artery, in accordance with a preferred embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 (not to scale) is a schematic cross-sectional illustration of an implant 42 comprising a membrane 40 and an expandable stent 30, in accordance with a preferred embodiment of the present invention. Preferably, membrane 40 is produced separately from stent 30, and is adapted for subsequent application to the stent. Further preferably, the membrane comprises a biocompatible, biostable, highly-elastic polyurethane, or other material suitable for long-term implantation in a site such as a coronary artery 20 of a human patient.

Typically, the generally cylindrical body of membrane 40 is mixed with or has applied thereto one or more drugs, which are intended, for example, to minimize the inflammatory response to implantation of stent 30 or to prevent restenosis of coronary artery 20. Advantageously, use of a polyurethane membrane as provided by this embodiment generally facilitates the formation and growth of an endothelial lining on the inner lumen of membrane 40 and/or of stent 30.

Notably, and unlike commercially-available stent-based drug-delivery systems for use in a coronary artery, membrane 40 is typically able to deliver a significant quantity of the one or more drugs, e.g., hundreds or several thousands of micrograms of each drug.

For some applications, membrane 40 comprises an inner layer 34 and an outer layer 36, each including a respective drug or combination of drugs. It is to be understood that, although two layers are shown in Fig. 1, the scope of the present invention includes the use of a membrane having a single layer as well as a membrane having three or more layers.

In a preferred embodiment, inner layer 34 of membrane 40 comprises an anti-proliferative drug, intended to reduce neointimal hyperplasia, while outer layer 36 comprises an anti-inflammatory drug, intended to facilitate the healing process of the tissue of coronary artery 20 following implantation of stent 30. As appropriate, other drugs, such as steroids, anti-thrombotic drugs, tissue growth regulating drugs, or agents for administering gene therapy may be integrated into membrane 40. Advantageously, whether one or two layers are used, covering stent 30 with membrane 40 typically inhibits that portion of the restenosis which occurs in some prior art coronary artery stents through the struts of these stents.

In embodiments employing single-layer or multi-layer membranes, the kinetics of the release of the one or more drugs is preferably controlled using techniques known in the general art of drug delivery. For example, membrane 40 may be configured such that one of the drugs is released over a time period spanning less than five hours, while another one of the drugs is released over a period greater than five hours, or even over days, weeks, or months, as appropriate.

For some applications, a plurality of micro-perforations 26 are formed in membrane 40 prior to the application of the membrane to stent 30. In such a perforated membrane, passage is facilitated of therapeutic

materials from the bloodstream 22 through the struts of stent 30, through the perforations, and to lesions 24 which may have formed around the stent implantation site. Three such perforations 26 (not to scale) are shown in Fig. 1, although it is to be appreciated that typically a very large number may be produced during the manufacture of membrane 40. Preferably, the perforation process is additionally configured so as to enhance the growth of the endothelial lining on the inner surface of stent 30, e.g., by permitting endothelial cell growth through the pores in membrane 40. Further preferably, pharmaceutical products incorporated into membrane 40 are utilized to inhibit smooth muscle cell proliferation (neointimal hyperplasia) on the inner surface of stent 30, which may lead to restenosis and thereby increase the likelihood of a second angioplasty procedure.

As appropriate, the perforation of membrane 40 may be performed mechanically, chemically, by laser, by radiation, or by other means known in the art. For some applications, a small quantity of a biodegradable polymer such as polylactic acid, polyglycolic acid, or a copolymer of lactic and glycolic acid is preferably incorporated into a solution from which membrane 40 is made. The polymer biodegrades either before or after implantation, thereby leaving small pores in the membrane. It is to be understood that various aspects of the perforation can be regulated by appropriate selection of the concentration of the biodegradable polymer, as well as by promoting the aggregation of the polymer in certain portions of the membrane.

Alternatively or additionally, other techniques known in the art may be used to perforate the membrane, such as the application of gamma radiation using techniques similar

to those used for perforating the Omiderm skin graft (Omiderm, Ltd., Israel).

Typically, membrane 40 is adapted to be applied to any of a range of commercially-available stents, for example, the NIR or NIROYAL stents, manufactured by Medinol, Israel, and distributed by Scimed of Boston Scientific, USA. Membrane 40 is preferably secured to stent 30 by a pressure fitting process, although it is to be appreciated that for many applications, other processes may be suitable.

For most applications, membrane 40 (comprising a single layer or a plurality of layers) is prepared in advance, preferably by a dip-coating process, and subsequently removed from the mandrel used for dip-coating and secured to stent 30. As appropriate, one or more drugs may be incorporated into the solution(s) in which the mandrel is dipped. By way of illustration and not limitation, for a two-layer membrane, the first solution may comprise an appropriate solvent, polyurethane grains and an anti-proliferative agent, while the second solution may comprise the solvent and polyurethane grains and an anti-inflammatory agent. Alternatively or additionally, one or more pharmaceutical products are applied to either or both surfaces of membrane 40 subsequent to the creation thereof.

Preferably, but not necessarily, membrane 40 comprises an elastomer such as Tecoflex 80A (Thermedics, USA), Chronoflex AR (Cardiotech, USA), or ElastEon 3 (Elastomedic Pty, Australia). These materials (as well as others known in the art which may be used in the membrane) are typically able to stretch more than 500% without suffering structural damage, and are therefore satisfactory for the considerably smaller strains induced during inflation of stent 30.

In experiments performed in accordance with a preferred embodiment of the present invention, two sets of three polyurethane membranes were produced by twice dip-coating either titanium or Teflon mandrels into solutions of dimethylformamide (DMF) or tetrahydrofuran (THF) solvents that contained Tecoflex 80A and 17% paracetamol by weight. The membranes were air-dried, and subsequently secured to 9 mm stents by pressure-fitting. Each membrane-stent assembly was inflated by a low pressure balloon, and immersed in separate 100 ml buffer solutions that were 0.1 M, pH 6-8, and maintained at 37 degrees C. Spectrophotometric analysis at 242 nm was performed on 5 ml samples of the solutions that were taken after five hours of gentle mixing, and indicated that approximately 1700 micrograms of the paracetamol, i.e., essentially all of the paracetamol, was released from each membrane within five hours. It is to be understood that other drugs, e.g., anti-proliferative drugs such as Rapamycin or Taxol, or any of the other pharmaceutical products described hereinabove may similarly be incorporated into membranes or applied to the surfaces of membranes provided by these embodiments of the present invention.

It is to be appreciated that although preferred embodiments of the present invention are described with respect to applying membrane 40 to stent 30, it is within the scope of the present invention to insert membrane 40 in a coronary artery without the use of a stent, to act as a drug delivery vehicle.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and sub-combinations of the various features described

hereinabove, as well as variations and modifications thereof that are not in the prior art which would occur to persons skilled in the art upon reading the foregoing description. For example, whereas membranes having desirable properties are described in the disclosure and recited in the claims, the scope of the present invention also includes methods for manufacturing such membranes, which are explicitly disclosed herein or which would occur to persons skilled in the art having read the disclosure of the present patent application.

CLAIMS

1. A membrane for implantation in a coronary artery of a patient, comprising a substantially-cylindrical elastomeric polyurethane body adapted for subsequent application to a coronary artery stent.

2. A membrane according to claim 1, wherein the body comprises at least one pharmaceutical product.

3. A membrane according to claim 2, wherein the body is adapted to release the at least one pharmaceutical product for at least twenty four hours following implantation of the membrane in the patient.

4. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises a pharmaceutical product applied to a surface of the membrane prior to implantation of the membrane in the patient.

5. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises a pharmaceutical product mixed into the body of the membrane.

6. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises an anti-inflammatory agent.

7. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises an anti-proliferative agent.

8. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises a steroid.

9. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises an anti-thrombotic agent.

10. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises a tissue growth regulating agent.

11. A membrane according to claim 2, wherein the at least one pharmaceutical product comprises at least two distinct pharmaceutical products.

12. A membrane according to claim 11, wherein the body comprises an inner surface, adapted to deliver to the patient a first one of the pharmaceutical products, and an outer surface, adapted to deliver to the patient a second one of the pharmaceutical products.

13. A membrane according to claim 12, wherein the first one of the pharmaceutical products comprises an anti-proliferative agent, and wherein the second one of the pharmaceutical products comprises an anti-inflammatory agent.

14. A membrane according to claim 1, wherein the body comprises:

an inner layer, comprising a first pharmaceutical product and adapted for subsequent application to the stent; and

an outer layer, disposed further from an axis of the cylindrical membrane than the inner layer, comprising a second pharmaceutical product different from the first pharmaceutical product.

15. A membrane according to claim 1, and comprising at least 100 micrograms of a pharmaceutical product, capable of passing from the membrane to the patient after implantation of the membrane in the patient.

16. A membrane according to claim 15, wherein the pharmaceutical product comprises at least 500 micrograms of the product.

17. A membrane according to claim 16, wherein the pharmaceutical product comprises at least 1000 micrograms of the product.

18. A cylindrical membrane for implantation in a patient, comprising:

an inner layer, comprising a first pharmaceutical product and adapted for subsequent application to a stent; and

an outer layer, disposed further from an axis of the cylindrical membrane than the inner layer, comprising a second pharmaceutical product different from the first pharmaceutical product.

19. A membrane according to claim 18, wherein the first pharmaceutical product comprises an anti-proliferative agent, and wherein the second pharmaceutical product comprises an anti-inflammatory agent.

20. A membrane according to claim 18, wherein the membrane is adapted to be implanted with the stent in a coronary artery of the patient.

21. A membrane for implantation in a patient, comprising a cylindrical polyurethane body adapted to be fixed to a coronary artery stent by pressure fitting and to be implanted with the stent in a coronary artery of the patient.

22. A membrane according to claim 21, wherein the membrane is adapted for pressure fitting to any one of a plurality of stents, each having a different respective physical characteristic.

23. A membrane for implantation in a patient, comprising a cylindrical, substantially-seamless polyurethane body adapted to be fitted to a coronary artery stent and to be

implanted with the stent in a coronary artery of the patient.

24. A membrane for implantation in a patient, comprising a cylindrical, preformed polyurethane body adapted to be fitted to a coronary artery stent and to be implanted with the stent in a coronary artery of the patient.

25. A membrane for implantation with a stent in a coronary artery of a patient, the membrane comprising a cylindrical polyurethane body having an inner surface treated so as to facilitate endothelial cell adherence thereto.

26. A membrane according to claim 25, wherein the body comprises a pharmaceutical product in a vicinity of the inner surface, which pharmaceutical product is such as to facilitate the adherence.

27. A membrane according to claim 25 or claim 26, wherein the inner surface is treated so as to inhibit neointimal hyperplasia (NIH).

28. A membrane according to claim 27, wherein the body comprises a NIH-inhibiting pharmaceutical product in a vicinity of the inner surface.

29. A membrane for implantation in a coronary artery of a patient, comprising a cylindrical body which comprises a pharmaceutical product and which is adapted for subsequent application to a stent, the body being adapted to release the pharmaceutical product for at least five hours following implantation of the membrane in the patient.

30. A membrane according to claim 29, wherein the body is adapted to release the pharmaceutical product for at least 24 hours following implantation of the membrane in the patient.

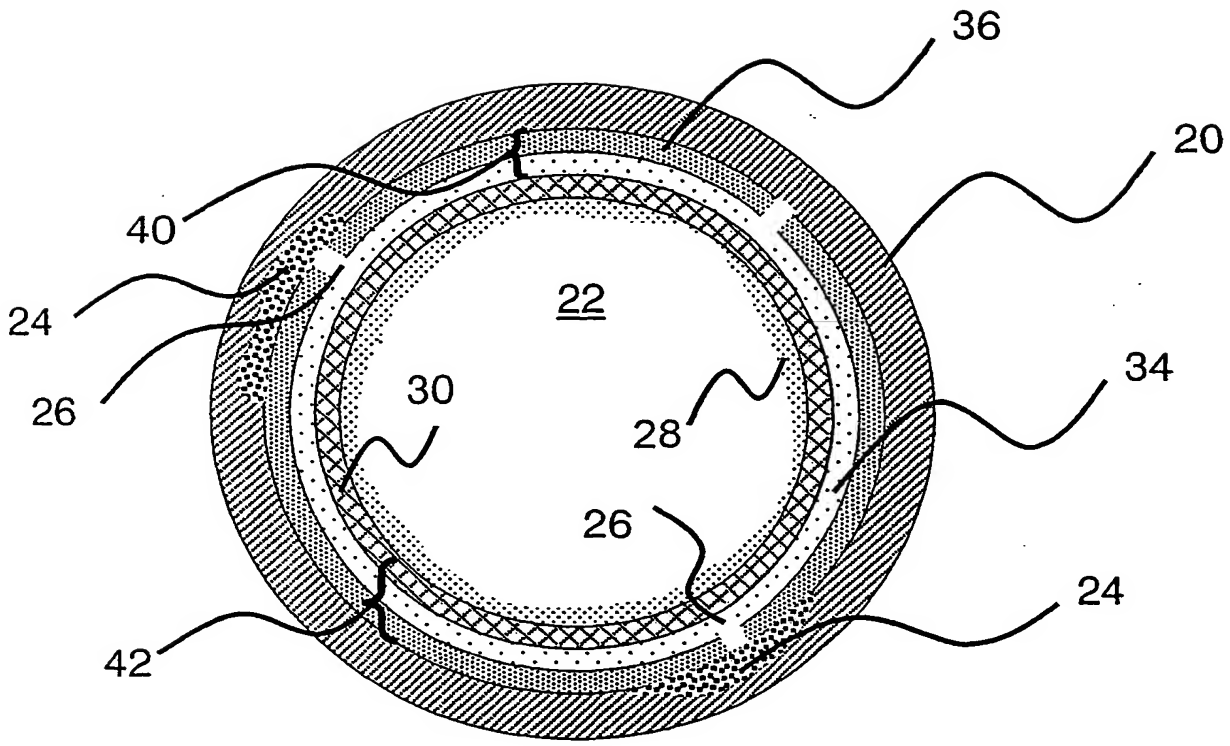
31. A membrane according to claim 30, wherein the body is adapted to release the pharmaceutical product for at least 72 hours following implantation of the membrane in the patient.

32. A membrane according to any one of claims 29-31, wherein the body comprises at least 500 micrograms of the pharmaceutical product.

33. A membrane for implantation in a coronary artery of a patient, comprising polyurethane and a biodegradable polymer selected from the list consisting of: polylactic acid, polyglycolic acid, and a copolymer of lactic and glycolic acid, a disposition of the biodegradable polymer in the membrane being such as to: (a) degrade the polymer following implantation of the membrane in the coronary artery, and (b) induce the generation of perforations in the membrane responsive to the degrading.

34. A membrane according to claim 33, wherein prior to implantation, a first portion of the membrane comprises a first concentration of the polymer and a second portion of the membrane comprises a second concentration of the polymer, different from the first concentration, the first and second concentrations being such as to induce different respective densities of perforations in the first and second portions of the membrane.

FIG. 1



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(71) Applicants *(for all designated States except US)*: **SHAYEN MEDICAL LTD.** [IL/IL]; 9 Hakotzer Street, 47411 Ramat Hasharon (IL). **KEREN, Gad** [IL/IL]; 11 Simcha Holzberg Street, Kiryat Ono 55022 (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARUCH, David** [IL/IL]; 9 Hakotzer Street, 47411 Ramat Hasharon (IL). **ROTMAN, Avner** [IL/IL]; 21 Eisenberg Street, 76289 Rehovot (IL).

(74) Agents: **SANFORD T. COLB & CO.** et al.; P.O. Box 2273, 76122 Rehovot (IL).

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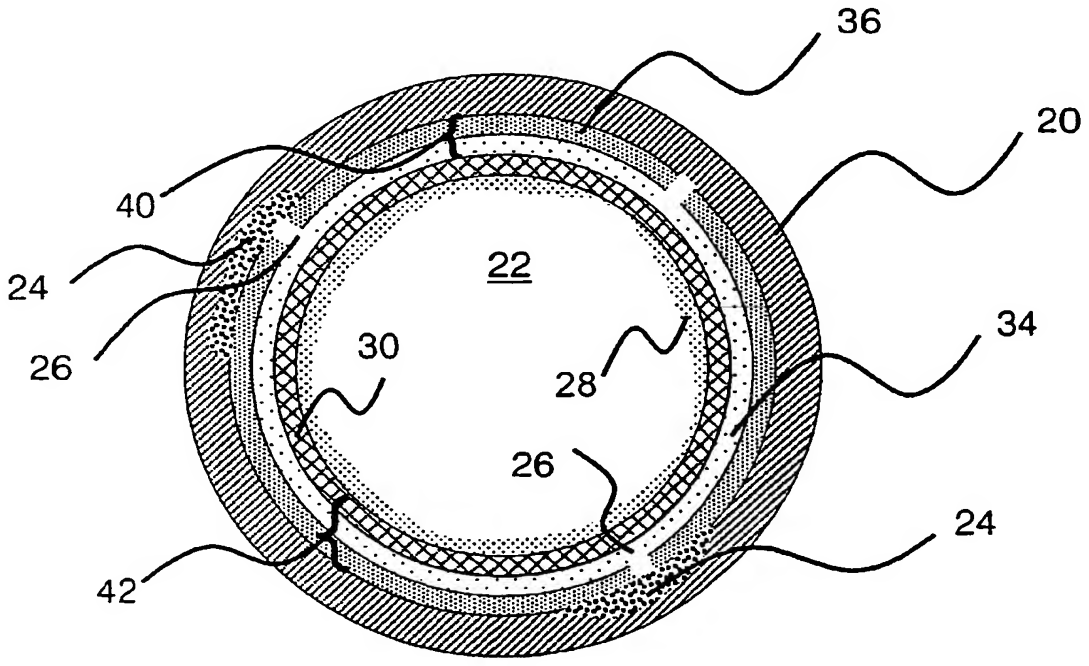
(54) Title: DRUG-ELUTING MEMBRANE FOR CORONARY ARTERY STENT



(57) Abstract: A membrane (40) is provided for implantation in a coronary artery (20) of a patient. The membrane preferably includes a substantially-cylindrical elastometric polyurethane body, adapted for subsequent application to a coronary artery stent (30). The body of the membrane typically includes one or more pharmaceutical products, e.g., an anti-inflammatory agent and an anti-proliferative agent, optionally disposed on different respective layers (34, 36) of the membrane.

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,464,650 A (BERG et al) 07 November 1995, see Abstract, column 4, lines 44-55; column 5, lines 26-28; column 6, line 61; column 7, lines 6-8; claims 1-22.	1-34NON

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